



MEETING REPORT

Consultation on Crimean-Congo haemorrhagic fever prevention and control

Stockholm, September 2008

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Stockholm, March 2009

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1 Background

The founding regulation (Regulation (EC) No 851/2004) establishing the European Centre for Disease Prevention and Control (ECDC) gives ECDC a mandate to strengthening the capacity of the European Union (EU) for the prevention and control of infectious diseases.

An ECDC-initiated assessment on the importance and magnitude of vector-borne diseases identified Crimean Congo haemorrhagic fever (CCHF) as a priority disease for the European Union. CCHF outbreaks constitute a threat to public health because of its epidemic potential, its high case fatality ratio, its potential for nosocomial outbreaks, and the difficulties in treatment and prevention. Within the EU, CCHF is currently only endemic in Bulgaria, but disease activity is documented in neighbouring countries (e.g. Albania, Kosovo, Russia, Turkey and Ukraine). The recent detection of a case in Greece highlights the risk for further geographic spread in the EU.

It is within this scope that ECDC called a multidisciplinary consultation of CCHF experts to update the main epidemiological, microbiological and clinical characteristics of CCHF, to review the areas at risk for introduction and spread of CCHF within Europe and to identify appropriate preparedness interventions on the European level. The one-day consultation brought together European experts in the field of infectious diseases, epidemiology, acarology, microbiology, case management and infection control, the European Commission Sanco C3 unit, and international experts from Russia, the United States and the World Health Organization, Regional Office for Europe (WHO EURO).

2 Objectives of the consultation

The objectives of this consultation were:

- to review the Crimean-Congo haemorrhagic fever Virus (CCHFV) epidemiological situation in Europe;
- to identify gaps for prevention and control; and
- to identify the role for ECDC in order to strengthen preparedness and response within in the European Union.

3 Expert presentations

After an introduction, presenting the results of the V-borne project (Call for tender 'Assessment of magnitude and importance of vector-borne diseases in Europe') and informing about the Arbo-ZooNet (International Network for Capacity Building for the Control of Emerging Viral Vector-Borne Zoonotic Diseases), updates on the epidemiologic situation/recent outbreaks of CCHF were presented from Bulgaria, Turkey, Greece and Russia. These presentations were followed by presentations on the current state on prevention and control in the European Member States.

3.1 V-borne project

Priorities for CCHF identified in the V-borne project for ECDC to take into consideration are:

Short-term priorities

- Endemic regions in countries with CCHF (south-eastern Europe) should be further mapped on national and international level and the degree of CCHF risk in all countries should be estimated.
- Awareness of general public about the disease in all endemic regions should be increased by launching general information campaigns, inclusive advice to people visiting areas with CCHF risk about how to avoid infection.
- Preventive measures should be recommended for countries where CCHF is endemic and for the non-endemic EU countries in case of imported acute CCHF cases.
- Approaches for diagnostic methods should be standardised and the assays validated.
- A standard programme should be planned to achieve knowledge of arthropod vector distribution and dynamics.
- Factors that trigger incidence and spreading of CCHF should be further identified (complex studies needed).

Long-term priorities

- Studies to better understand and reveal the natural cycle of CCHF virus.
- Collection of epidemiological data based on:
 - examination of vectors and reservoir hosts for the presence of CCHF virus by using standard, especially molecular diagnostic techniques;
 - seroprevalence studies of people exposed to ticks and of indicator animal hosts living in regions where the vectors are distributed;
 - description of clinical cases inclusive their complete aetiology and geographical location;
 - further evaluation and classification of environmental conditions that can influence the spatio-temporal distribution and dynamics of CCHF.
- Introduction of a standard programme to predict tick activities in European countries.
- Plan a randomised clinical trial to ascertain the benefits of ribavirin treatment.
- Plan basic research on possible additional antiviral drug therapy and/or vaccine.
- Further research on investigations of CCHF pathogenesis.

3.2 Arbo-ZooNet

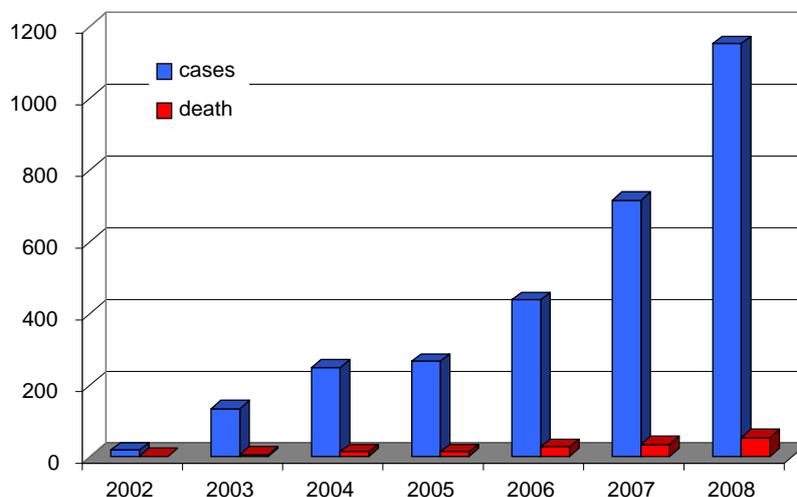
- Arbo-ZooNet is an EU Seventh Framework Programme project that covers CCHF, West Nile fever and Rift Valley fever.
- Coordinator: Michele Bouloy.
- It is comprised of 25 partners (including partners from Asia, China, South Africa, Senegal, Mauritania).
- The three-year project (2008–2011) is a coordinated research programme including key laboratories aimed at improving the EU's response to outbreaks of these diseases.
- There are seven interrelated work packages:
 - WP 1: Coordination, management, review and assessment;
 - WP 2: Geographical and temporal risk assessment;
 - WP 3: Capacities and Proficiency in Diagnosis and Detection;
 - WP 4: Surveillance;
 - WP 5: Establishment of virulence standards;
 - WP 6: Intervention strategies; and
 - WP 7: Knowledge dissemination and technology transfer.

- The biggest reported outbreak occurred in 1954–1955 with a total of 487 cases (213 in 1954 and 274 in 1955) with about 300 cases alone in the region of Shumen in the north-east of Bulgaria.
- Between 1953 and 1974, a total of 1 101 cases were notified with a lethality of 17%, among them 20 nosocomial infections.
- Between 1975 and 1996, a total of 271 cases were notified with a lethality of 11%. A human vaccine was used for prophylaxis of persons at risk.
- Since 1997, 196 suspected or confirmed cases were notified with a lethality of 22%.
- In April 2008, six probable CCHF cases were reported in the municipality of Gotse Delchev, in Blagoevgrad district, an area in the south-west, bordering Greece and Macedonia, among them one nosocomial infection in a healthcare worker.

3.4 Situation in Turkey

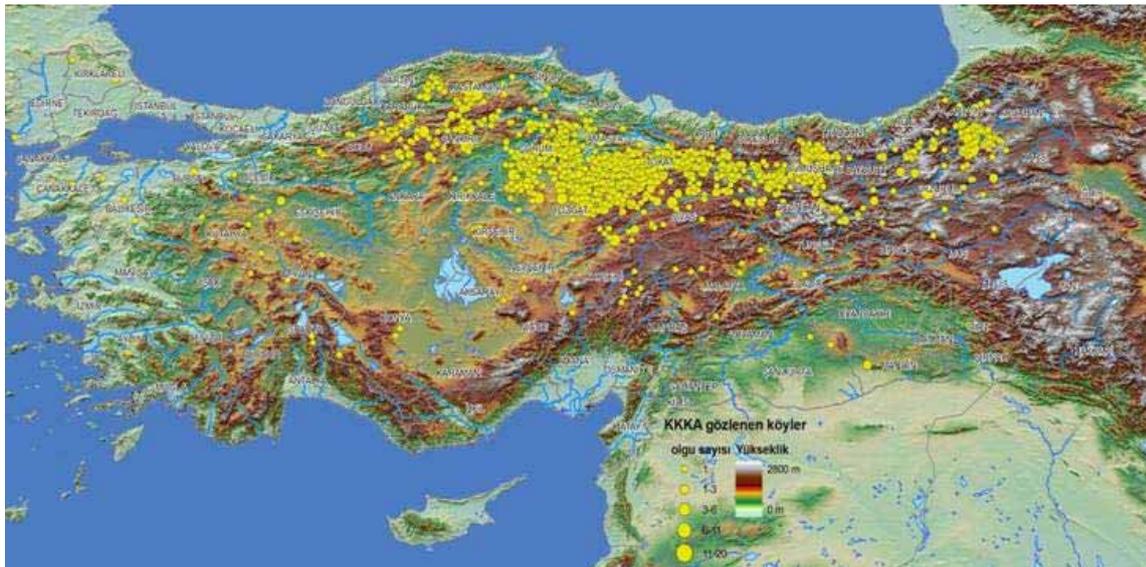
- Increase in number of cases notified/deaths by year (Source: Onder Ergonul): 2002 [17/0]; 2003 [133/6]; 2004 [249/13]; 2005 [266/13]; 2006 [438/27]; 2007 [1154/54]*; partial data (Figure 3).
- Case definition, see Appendix 3.

Figure 3: Number of CCHF cases in Turkey, 2002-2008*



- Case fatality ratio remains stable, ranging between 4% and 6%.
- Since 2003, 13 cases have been documented in healthcare workers, with three deaths following exposure to blood and/or body fluids.
- A sero-epidemiological study in 1974 found evidence of anti-CCHF antibodies in 26/1100 (2.4%) sera tested in Turkey, however without any clinical case reported.
- The first symptomatic human case was identified in 2002.
- Initially cases have been reported from the European part (related to the orphan Greek isolate strain AP92).
- Currently cases are essentially described in adults exposed to tick bites during rural activities in north-central Anatolia (Figure 4). However, between 2002 and 2008 the number of CCHF cases also increased in the rural areas in the east and northeast of the country.
- The mode of dissemination of disease is not clear.

Figure 4: Distribution of confirmed CCHF cases in Turkey, 2002–2008



- A serologic study performed in an endemic area in Turkey revealed that the infection and attack rates can be very high in endemic areas (Source: Onder Ergonul):
 - Among 55 individuals tested (including 30 involved in husbandry), the overall infection rate was as high as 0.27 (15/55). Among individuals with history of tick bite the infection rate was 0.42 ($p=0.046$) and the attack rate 0.20 (11/55), meaning that one out of every five persons living in this endemic area and one out of two persons with tick bite history in endemic area acquired the disease.
- The disease is mostly active between April and September.
- A predictive model to map the habitat suitability for the vector tick was developed by Estrada-Pena et al. from satellite-based climate data and high-resolution features of the vegetation from Landsat images of Turkey. It was found that areas of higher risk (higher CCHF reporting) were correlated ($p<0.05$) with zones of high climate suitability for the tick together with a high rate of fragmentation of agricultural land interspersed between forest and shrub-type vegetation.
- The CCHF virus strain in circulation in Turkey is closely related to the Balkan strains.
- There is an ongoing controversial discussion about the therapeutic use of ribavirin.
- Healthcare workers that have been in contact (e.g. needle stick injury, splash of blood to mucosal surfaces such as eyes, mouth and nose) with a probable or confirmed case are offered ribavirin prophylaxis.
- Convalescent sera are used for treatment of patients.

3.5 Situation in Greece

- On 26 June 2008, the Hellenic Centre for Diseases Control and Prevention (HCDCP) was notified about a 46-year-old female case of CCHF that occurred in a village near the city of Komotini in the Prefecture of Rhodopi in northern Greece (Figure 5).
- The woman died on day five (25 June).
- The diagnosis was made by RT-PCR and the CCHF virus isolated belonged to the Balkan strains.

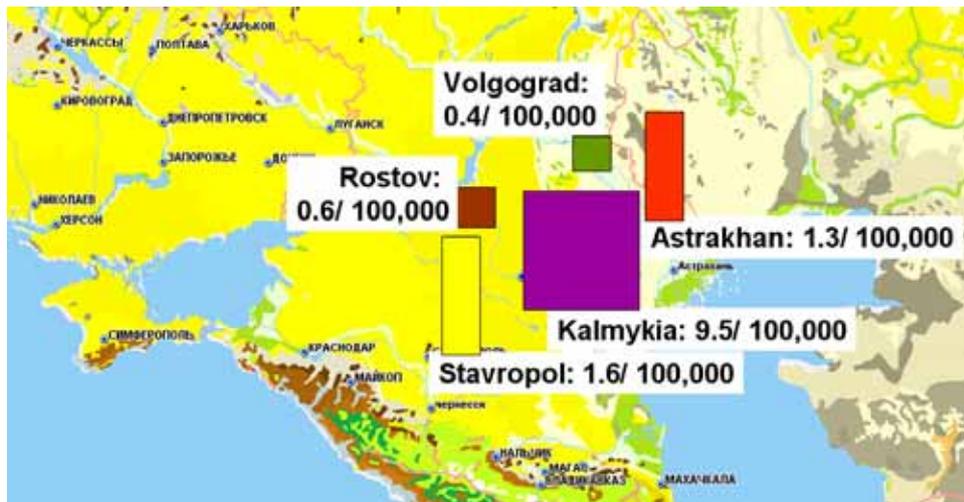
Figure 5: Localisation of the confirmed CCHF case, Greece, 2008

- A case definition was developed (see Appendix 3) and contact tracing was initiated.
- Guidance for management of a CCHF case within a hospital (including isolation of case, if possible in a negative pressure room) was provided.
- The administration of ribavirin within 3-4 days from the onset of symptoms was considered, according to WHO guidance.
- Guidance for disinfection, handling and transport of clinical specimen, accidental needle stick injuries, blood contact, and management of dead bodies was developed.
- Information about CCHF mode of transmission, measures for the prevention of tick bites and proper removal of attached ticks was distributed to the residents of the Prefecture of Rhodopi and to healthcare centres and hospitals.
- Surveillance of human cases was intensified.
- Surveillance, performed from June to September 2008, detected 15 suspected cases; however, all tested negative for CCHF virus.
- There are no other identified cases to date.
- Surveys of humans, domestic animals and ticks have started.
- Several seroepidemiological studies conducted between 1970 and 1980 provided evidence for CCHF virus circulation in Greece:
 - In 1976, the AP92 strain was isolated from an asymptomatic veterinarian who acquired a laboratory infection with this strain.
 - AP92 strain was isolated from *Rhipicephalus bursa* ticks from goats in Vergina, a village in northern Greece, about 80 km west of Thessaloniki.
 - This strain is up to date the most divergent of the CCHF virus strains.
 - The pathogenicity of this strain for humans needs to be further investigated.
- Between 1980 and 1981, serosurveys revealed that four out of 65 inhabitants (6.1%) of the Vergina region had evidence of previous CCHF infection without history of severe disease resembling CCHF.
- A serosurvey of 3 388 healthy farmers, wood cutters and shepherds throughout Greece conducted between 1981 and 1988 revealed overall 1.1% antibodies for AP92, ranging from 0% to 6.3%.
- Since 1982, 409 serum samples were taken from patients with clinical picture resembling CCHF. None of the patients were found positive.
- Survey of domestic animals from northern Greece in the 1980s revealed low prevalence for CCHF.
- Survey of 3 249 ticks collected from domestic animals in prefectures in northern Greece (Macedonia and Thrace region) between 2003–2006 showed the following distribution: *Ixodes ricinus* 44% (9/11 provinces); *Rhipicephalus bursa* 19.15% (all provinces); *Hyalomma marginatum* 12.4% (all provinces). All were tested CCHF negative.

3.6 Situation in Russia

- CCHF outbreaks have been reported in the following regions of the Russian Federation: Astrakhan, Rostov, Volgograd regions, Kalmykia, Krasnodar and Stavropol territories, Dagestan and Ingushetia. Between 1963 and 1971 there were 334 cases alone reported from Rostov, with a case fatality of about 15%.
- Between 2000 and 2008 more than 1 150 clinical CCHF cases (50 deaths) were diagnosed in Russia.
- The majority of the cases occur in three of the 13 oblasts of the Southern Federal district: Republic of Kalmykia, Rostov oblast and Stavropol kraj, with the highest incidence between 2000 and 2008 in Kalmykia (Figure 6).

Figure 6: Annual incidence rate of CCHF in Russia, 2000–2008



- In the northern Volgograd province, the number of cases appears to be weather dependent, e.g. the number of cases increases in years that have a mild winter followed by a hot summer.
- In the southern Stavropol, this pattern cannot be observed.
- In Stavropol and Astrakhan, 25–35% of cases develop severe disease, 60–70% moderate, and 5% mild disease. Around 60–90% of cases present with some kind of haemorrhagic manifestation.
- Viral load correlates with the severity of CCHF (day three to day five of hospitalisation).
- The yearly case fatality rate in confirmed cases ranges from 1.7% to 11.1%, with an overall case fatality rate of 3.2% for the period of 2002–2008.
- Modes of transmission are tick-bite (60–70%); rural activity, not further specified (15–25%); contact with infected blood while butchering (10–12%); and nosocomial transmission (1%).
- Specific laboratory diagnostics is performed on:
 - All persons in an endemic region in Russia, who report a tick bite or contact with a CCHF patient who develop fever within two weeks after exposure. They should be hospitalised.
 - All persons hospitalised with fever in the epidemic season (April–August) and presenting with CCHF-like clinical symptoms.
 - All travellers from endemic regions during the epidemic season, if hospitalised with CCHF-like clinical presentation or reported tick bite and fever.
- The case definition is based on laboratory: high titre of specific IgM (>400) and/or ELISA — four-fold (or more) increase of specific IgG titre (e.g. from 100 to 400) — and/or specific PCR (positive result) (see Appendix 3).
- The PCR assay (“AmpliSens®CCHF”), developed and manufactured by the Central Institute of Epidemiology, has been compared to the IgM-capture ELISA and showed a good clinical sensitivity (95-100%) and clinical specificity (at least 98%).
- There are two genotypes circulating in the former Soviet Union: the European genotype, prevalent in Russia, and the Chinese genotype (coming along the “Silk Road”), detected e.g. in Kazakhstan.
- Surveys of 792 suspected CCHF cases in Astrakhan (2000–2006) and 1 379 suspected CCHF cases in Rostov (2000–2005) revealed 11% and 3%, respectively, of laboratory positive cases.
- The ribavirin used is from European producers.
- There is a bank of convalescent serum (from people infected more than three years ago). The serum is used for post-exposure prophylaxis. Donor selection follows the command of the Ministry of Public Health.

4 Discussion of the current state on prevention and control in the European Member States

4.1 Diagnostic capacity

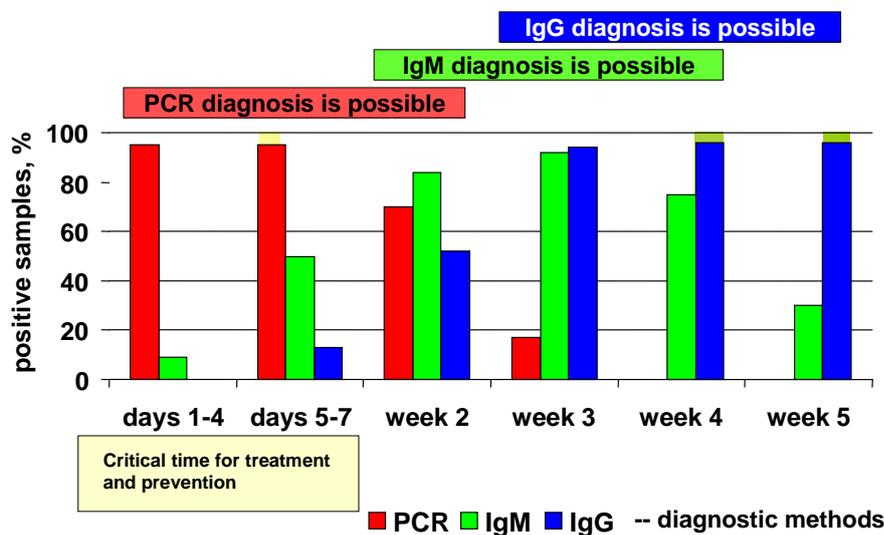
European Network of Diagnostics for Imported Viral Diseases (ENIVD)

- The network includes 42 members from 27 countries, including BL3 and BL4 laboratories.
- Public website: www.enivd.org
- Communication/email list management using listserv.
- EQA studies performed for other viral haemorrhagic fever viruses (hantavirus, dengue, filovirus, Lassa), but not yet for CCHF.
- CCHF cases imported to Europe:
 - 1998 (fatal) Zimbabwe–UK
 - 2001 (tourist) Bulgaria–Germany
 - 2004 (repatriation) Senegal–France

CCHF diagnostics

- In-house tests include IFA, EIA, WB, HIA, RT-PCR and virus isolation.
- CCHF diagnosis relies on both RT-PCR and serology (see Figure 7).

Figure 7: Laboratory diagnostic of CCHF (A Platonov, Russia)



- Commercial IFA tests:
 - CCHF IgG Sandwich ELISA (Biological Diagnostic Supplies Limited, BDSL®).
 - IFA test based on recombinant antigens GPC and N / biochip technology, under evaluation (Euroimmun®).
- PCR assay AmpliSens® CCHF:
 - Developed and manufactured by Central Institute of Epidemiology, Russia.
 - Specific for CCHF virus RNA.
 - Target: S segment RNA; internal control included.

- Detection limit: 5×10^3 copies/ml of serum/plasma: 2×10^4 copies/ml of tick suspension.
- Sensitivity: 100%, when tested using CCHF isolates of different genotypes.
- Clinical sensitivity: 95–100% in comparison with IgM-capture ELISA.
- Specificity: 100%, when tested including Dugbe/Nairovirus; Inkoo & Tahyna /Orthobunyavirus; VEE & Sindbis /Alphavirus; Kemerovo/ Orbivirus; Dhori/ Thogotovirus; West Nile virus, tick-borne encephalitis virus, Omsk haemorrhagic fever virus/flavivirus; enteroviruses; rickettsia; *Neisseria meningitidis*, etc.
- Clinical specificity: at least 98% in comparison with IgM-capture ELISA.

Diagnostic capacity in the EU

According to ENIVD (www.enivd.org) these are the laboratories within 14 Member States and one accession country that perform CCHF diagnostics:

- Belgium
 - Prins Leopold Instituut voor Tropische Geneeskunde, Antwerp: [IFA]
- Bulgaria
 - National Centre for Infectious and Parasitic Diseases, Sofia: [IFA, PCR, VI]
- Germany
 - Bernhard-Nocht Institut, Hamburg: [IFA, EIA, PCR, VI, EM]
 - Marburg University, Marburg: [PCR]
 - Institut für Mikrobiologie der Bundeswehr, München: [IFA, PCR]
- Spain
 - Instituto Carlos III, Madrid: [PCR]
 - Laboratorio de Microbiologia, Hospital St. Maria Nai, Orense: [IFA, EIA]
- France
 - Institut Pasteur, Lyon: [IFA, EIA, PCR, VI]
 - Laboratoire de Virologie, Hospital la Timone, Marseille: [PCR]
 - Unité des Virus Emergents, Timone University, Marseille: [IFA, EIA, PCR]
- Finland
 - Haartman Institute, University of Helsinki: [PCR, IFA]
- Great Britain
 - Health Protection Agency, Colindale: [IFA, PCR, VI]
 - Health Protection Agency, Porton Down: [IFA, EIA, PCR, VI]
- Greece
 - Aristotle University, Thessaloniki: [IFA, PCR, VI]
- Hungary
 - National Center for Epidemiology, Budapest: [EIA]
- Italy
 - Istituto Nazionale per le Malattie Infettive, Rome: [IFA, NT, PCCR, VI]
- The Netherlands
 - Erasmus MC, Dept of Virology: [EIA]
- Sweden
 - Swedish Institute for Infectious Disease Control, Karolinska Institute Stockholm: [IFA, NT, PCR]
- Slovenia
 - University of Ljubljana: [IFA, EIA, PCR, VI]
- Slovakia
 - Institute of Virology/Institute of Zoology, Slovak Academy of Sciences: [HIA]
- Accession country: Turkey
 - Refik Saydam Hygiene Institute, Ankara: [EIA, PCR]

Limitations

- Transfer of EQA material is often problematic (import and export permit are needed).
- Shipping with licensed companies is expensive and their service is not available in all countries
- Movement of clinical material is also difficult.
- There is limited diagnostic capacity in the endemic areas.
- There is not sufficient well-documented material (sera, isolates) that could be used for external quality assurance.
- There are no simple and rapid diagnostic tests for early treatment decisions.

4.2 Case management and vaccination

Antiviral drugs – ribavirin

- Ribavirin is on the WHO essential medicines list (15th Model List of Essential Medicines, March 2007).
- Although there is some evidence for its effectiveness in vitro, clinical efficacy needs to be assessed.
- Confounders within clinical outcome studies of ribavirin are:
 - E.g. severity of the infection, number of days from onset of symptoms, ineffective application (gastrointestinal symptoms — oral versus intravenous application affect pharmacological efficacy), duration of treatment, inclusion criteria.
- Randomised clinical trials for ribavirin are promoted under coordination of WHO. In order to assess the efficacy of ribavirin protocols in multi-centre studies, participants would first need to agree upon:
 - selection of controls;
 - treatment guidelines (doses, formulation, severity of disease, timing of ribavirin, administration);
 - oral versus intravenous ribavirin; and
 - post-exposure prophylaxis for patients who have had definite exposure to CCHF virus or infected tissue — e.g. a needle stick injury with the blood of a CCHF patient.
- Problem: randomised control trials involving placebo are regarded as unethical.

Immunoglobulins

- Bulgaria is using specific hyperimmune globulin (CHF Bulin®) from plasma of convalescents. They are used for: prophylaxis of persons who had contact with suspected CCHF patients, prophylaxis of suspected CCHF patients with clinical symptoms, treatment of CCHF patients, and prevention of bioterrorism.
- The protocol is:

Prophylaxis	3 ml
Suspected case	6 ml
Confirmed case	6-9 ml (day 1)
	6-9 ml (day 2–5 or until therapeutic effect is achieved)

New treatment strategies

- Interferons and interferon-stimulated antiviral proteins:
 - MxA (interferon-induced GTPases)
- Antibodies to CCHF:
 - Gammaglobulin obtained from immunisation of horses
 - Development of monoclonal antibodies would allow better control

Vaccine

- There is no vaccine licensed for the use in all EU Member States.
- An inactivated suckling mouse brain vaccine is used for prophylaxis of defined risk groups in Bulgaria.

Nosocomial infections

- Nosocomial infections were documented in Albania, Bulgaria, Kosovo, Turkey, Russia etc.
- The risk behaviours/procedures are not well studied.
- The use of standard infection control precautions (blood safety, injection safety, barrier nursing) needs to be reinforced.

4.3 Vector surveillance and control

Integrated Consortium on Ticks and tick-borne Diseases (ICTTD)

- ICTTD is an EU coordinated action consisting of a consortium of 44 institutions in 28 countries (started in 1996, until September 2009).
- Objectives are:
 - to contribute to a better understanding of tick–host–pathogen interactions;
 - to identify means of improved control of ticks and tick-borne diseases, including zoonoses;
 - to provide a forum for genomics, biosystematics, molecular diagnostics, epidemiology and remote sensing (tick identification CD, tick identification guide);
 - to develop an integrated database for ticks, hosts and pathogens (THPbase); and
 - to publish the ICTTD newsletter each quarter to disseminate information collected and published research worldwide.
- Webpage: www.icctd.nl

CCHF vectors

- Ticks of the genus *Hyalomma* parasite domestic and wild mammals and birds, and are abundant in semi-arid zones.
- This genus comprises 30 species, most undergoing a two-host cycle.
- Adult ticks prefer cattle and immature scrub hares.
- The ticks run actively from their resting sites, when a host approaches.
- Population dynamics depends on climatic factors — ecologic changes — wildlife and human factors.

Distribution of the three main vectors of CCHF in Europe

- *H. marginatum marginatum*: Albania, Bulgaria, Cyprus, France, Greece, Italy, Kosovo, Moldavia, Portugal, Romania, Russia, Spain, Ukraine, former Yugoslavia.
- *H. marginatum rufipes*: Macedonia, Russia, Ukraine.
- *H. marginatum turanicum*: unknown.

Individual *H. marginatum* ticks have recently been found in Germany and in the Netherlands (unknown mode of introduction)

Methods of control for *Hyalomma* ticks

- Eradication (not feasible)
- Ectoparasitica: acaricidal control
- Genetically resistant animals
- Movement control of infected animals
- Anti-tick vaccines
- Pheromone-based tick control
- Integrated control of ticks

It has been shown that where wild animals run with domestic animals (cattle) tick control on cattle will also reduce tick burden on the wild animals.

5 Concluding views from the participating experts

Based on the expert presentations and discussions, it was concluded that it is imperative to develop integrated control measures that include vector control, vaccination programmes, improved therapy strategies, diagnostic tools and surveillance, public awareness, capacity building and improvement of infrastructure in endemic regions. To achieve this it, it will be important for Member States and ECDC to link up to existing research networks and to foster collaboration with international partners like the World Health Organization (WHO) or the World Organisation for Animal Health (OIE).

The experts agreed that the surveillance of human CCHF cases should be strengthened. The development and the use of a standardised case definition between Member States would allow comparison of case reports. Rapid detection and confirmation of cases are essential to limit the spread of human disease. In this regard, the implementation of alert systems in endemic areas in slaughterhouses and hospitals, for example, has been shown to be useful. In addition, a strong laboratory capacity is important in endemic areas and areas where the virus could be expected to circulate. The ECDC-funded European Network for Diagnostics of Imported Viral Diseases — Collaborative Laboratory Response Network (ENIVD-CLRN) can provide assistance in sharing protocols and materials and in performing external quality assurance. Finally, considering the risk in these specific contexts, raising awareness of disease detection in rural settings, as well as of nosocomial transmission should be strengthened. The development of rapid diagnostic tests that can be used by clinicians to support making early treatment decisions is an important public health area for further research.

Information drawn from vector and animal surveillance is crucial for predicting human risk for CCHF infection but also for other tick-borne diseases. Therefore, the standardisation of protocols for tick collection from animals, their identification and screening for possible human pathogens would be helpful; diagnostic capacity would need to be developed accordingly. Areas of risk for the establishment of the vector, considering climatic and ecological conditions in Europe, need to be identified and vector surveillance need to be strengthened respectively.

In risk areas, raising public awareness of the risk of tick bites, the safe and rapid way to remove ticks, and the appropriate use of repellents is an essential element of preventive activities. The risk of disease transmission to healthcare workers is of particular importance and requires continuous training on transmission-based infection control precautions and the recognition of high risk procedures. The curative use of ribavirin remains to be further elucidated, and the development of vaccines should be supported.

Strengthening further collaboration with different stakeholders, e.g. WHO and OIE, as well as with existing networks such as ENIVD-CLRN, the International Network for Capacity Building for the Control of Emerging Viral Vector Borne Zoonotic Diseases (Arbo-ZooNet), will ensure the multidisciplinary approach in preparing and responding to the threat posed by CCHF.

Multidisciplinary research will allow better understanding of the epidemiology of CCHF in ticks, domestic livestock and wild animal populations, and will support the identification of human risk factors for infection and the development of better diagnostics, antiviral drugs and vaccines. Also, the identification of an animal model for testing would facilitate any further research, and allow studying host response to infection and evaluating intervention and control strategies. Finally, the role of environmental change, including climate change, needs further assessment.

Appendix 1: Participants

Lyubena Georgieva Andonova-Marinova	Medical University Sofia, Bulgaria
Roberta Andraghetti	World Health Organization, Regional Office for Europe
Marie-Christine Avargues	European Commission, DG Sanco C3
Michele Bouloy	Institut Pasteur, France
Onder Ergnonul	Marmara University, Turkey
Frans Jongejan	Utrecht University, The Netherlands
Nikolay Zlatkov Kalvatchev	National Centre of Infectious and Parasitic Diseases, Bulgaria
Helena Maltezou	Hellenic Centre for Disease Control and Prevention, Greece
Stuart Nichol	Centers of Disease Control and Prevention, Atlanta, USA
Matthias Niedrig	Robert Koch Institut, Germany
Alexander Platonov	Central Research Institute of Epidemiology, Russia
Gail Thomson	Health Protection Agency, United Kingdom

Appendix 2: Agenda of the consultation

ECDC – Stockholm, 19 September 2008

09:00 – 09:10	Opening of the meeting
09:10 – 10:00	Results of the V-borne project: Mapping the risk for the EU (Herve Zeller)
10:00 – 10:40	Update on the CCHF situation/recent outbreaks in Europe <ul style="list-style-type: none"> • Bulgaria (Nikolay Zlatkov Kalvathev) • Turkey (Onder Ergnonul)
10:40 – 11.00	Break
11:00 – 11:40	Update on the CCHF situation/recent outbreaks in Europe (continued) <ul style="list-style-type: none"> • Greece (Helena Maltezou) • Russia (Alexander Platonov)
11:45 – 12:30	Current state on prevention and control in the European Member States <ol style="list-style-type: none"> 1. Diagnostic capacity (Matthias Niedrig)
12:30 – 13:30	Lunch
13:30 – 14:15	Current state on prevention and control in the European Member States (continued) <ol style="list-style-type: none"> 2. Case management and vaccination (Lyubena Georgieva Andonova-Marinova)
14:15 – 15:00	<ol style="list-style-type: none"> 3. Vector surveillance and control (Frans Jongejan)
15:00 – 15:15	Break
15:15 – 15:45	Next steps
15:45 – 16:00	Conclusions of the meeting

Appendix 3: Case definitions

Bulgaria

Clinical description

An illness of gradual onset with acute high fever, chills, myalgia, nausea, anorexia, vomiting and backache. Haemorrhagic manifestation may follow.

Laboratory criteria for diagnosis

- Virus isolation
- Detection of CCHF virus nucleic acid
- Positive serology, which may appear late in the course of the disease

Possible case

N/A

Probable case

A clinically case with an epidemiological link (e.g. tick bite in endemic areas; contact with blood, biological fluids and tissues of possibly infected person and/or animal).

Confirmed case

A clinical case that is laboratory confirmed.

Greece

Suspected case

A patient with:

- abrupt-onset of high fever (>38.5°C) and one of the following symptoms: severe headache, myalgias, nausea, vomiting, and/or diarrhoea

AND

- history of tick bite within 14 days prior to the onset of symptoms
or
- history of contact with tissues, blood or other biological fluids from a possibly infected animal (e.g. abattoir workers, livestock owners, veterinarians) within 14 days prior the onset of symptoms
or
- healthcare workers in healthcare facilities, with a history of exposure to a suspect, probable or laboratory confirmed CCHF case, within 14 days prior the onset of symptoms

AND

- the contact/exposure took place in the Prefecture of Rhodopi (the Prefecture where the first CCHF case occurred in Greece).

Probable case

A suspected CCHF case fulfilling in addition the following criteria:

- thrombocytopenia

AND

- two of the following haemorrhagic manifestations: haematoma at an injection site, petechiae, purpuric rash, rhinorrhagia, haematemesis, haemoptysis, gastrointestinal haemorrhage, gingival haemorrhage or any other haemorrhagic manifestation in the absence of any known precipitating factor for haemorrhagic manifestation.

Confirmed case

A case that fulfils the criteria for probable CCHF case and in addition was laboratory confirmed at the World Health Organization (WHO) Collaborative Centre for Reference and Research on Arboviruses and Hemorrhagic Fever Viruses (Aristotle University of Thessaloniki, Thessaloniki, Greece) with one of the following assays:

- detection of IgM specific antibodies against CCHF virus or increase of IgG specific antibodies against CCHF virus between two serologic specimens (acute and convalescence phases);
- detection of CCHF virus genome in a clinical specimen using the molecular method RT-PCR followed by sequencing; or
- CCHF virus isolation.

Pakistan

Source: Guidelines for Crimean-Congo Hemorrhagic Fever developed with joint collaboration of Ministry of Health (MoH) –Government of Pakistan, National Institute of Health (NIH), Islamabad, and World Health Organization (WHO) — Update January 2005, available from: <http://nih.org.pk>

Suspected case

Patient with sudden onset of illness with high fever over 38.5°C for more than 72 hours and less than 10 days, especially in CCHF endemic areas and among those in contact with sheep or other livestock (shepherds, butchers, and animal handlers). Note that fever is usually associated with headache and muscle pains and does not respond to antibiotic or anti-malarial treatment.

Probable case

- Suspected case with acute history of febrile illness 10 days or less,
AND
- thrombocytopenia less than 50 000/mm³
AND
- any two of the following: petechial or purpuric rash, epistaxis, haematemesis, haemoptysis, blood in stools, ecchymosis, gum bleeding, other haemorrhagic symptom
AND
- no known predisposing host factors for haemorrhagic manifestations.

Confirmed case

Probable case with positive diagnosis of CCHF in blood sample, performed in specially equipped high bio-safety level laboratories, i.e.:

- confirmation of presence of IgG or IgM antibodies in serum by ELISA;
- detection of viral nucleic acid in specimen by PCR;
- isolation of virus.

Russia

The diagnosis MUST be based on laboratory findings:

- ELISA: high titre of specific IgM (> 400); and/or
- ELISA: four-fold (or more) increase of specific IgG titre (e.g. from 100 to 400) and/or specific PCR (positive results).

Turkey

Suspected case

Individuals who had fever, myalgia, malaise, diarrhoea, and history of being in endemic area

- Tick exposure history; and/or
- Residency or travel to CCHF endemic region
- Healthcare workers, exposure to blood and body fluids of a patient

Probable case

Suspected cases who had thrombocytopenia, elevated AST and ALT levels.

Confirmed case

CCHF IgM or PCR positivity in the blood or body fluids of the patient.

Appendix 4: Bulgarian CCHF vaccine

Source: <http://www.bulbio.com/CHF.html> (accessed on 18 February 2009)

ANTI-CHF VACCINE	
CRIMEAN HAEMORRHAGIC FEVER VACCINE, INACTIVATED	
COMPOSITION	
One dose of the vaccine (1 ml) consist of:	
Active substance:	
Inactivated antigen (CHF virus strain V 42/81) with titre in RBC	not less than 1:300
Auxiliary substances:	
Aluminium hydroxide	aluminum 0.8 mg/ml
Thiomersal	0.2 mg/ml
Sodium hydrogen carbonate	0.38 mg/ml
Sodium chloride	8.5 mg/ ml
Phenol red as indicator	0.2 mg/ml
Tobramycin	Traces
Water for injection	q. s. 1 ml
DOSSAGE AND PACKAGE	
The vaccine is an injection suspension (for subcutaneous injection) of 1 ml – 1 dose. In one secondary package there are 50 ampoules.	
PHARMACO-THERAPEUTIC GROUP OR EFFECT	
The vaccine builds specific active protective immunity against the CHF virus — 14 days after the first injection. The appearance of complement-binding antibodies is established.	
THERAPEUTIC INDICATIONS	
The vaccine is designed for the protection against infection with the CHF virus for persons over 16 years of age (boarder army units, medical workers, agricultural workers and other persons living in CHF endemic regions).	

CONTRAINDICATIONS

- acute infectious diseases, including during the period of convalescence, 30 days after the clinical symptoms
- febrile conditions
- active form of tuberculosis
- decompensated heart disease
- diabetes, thyrotoxicosis and adrenal insufficiency in decompensation phase
- acute phlogistic diseases of the central nervous system – meningitis, encephalitis, meningoencephalitis
Recovered patients of CHF need no immunisation
- Chronic or active hepatitis and liver cirrhosis
After entering clinic and biochemical remission, immunisation is allowed after consultation with a specialist
- Acute glomerulonephritis
The immunisations are to be deferred until the sixth month after recovery
- Neurotic syndrome
The immunisations are to be deferred until the corticosteroid treatment is brought to an end
- Allergy
 - children with direct hereditary allergies (parents, other children in the family) are to be immunised under the protection of antiallergic means;
 - contraindications of immunisation are anamnestic data of shock, oedema of Quince and other severe allergic reactions to allergens contained in the vaccines.
- Autoimmune diseases

SPECIAL PRECAUTIONS FOR USE

The immunisation is to begin after an examination by a physician.
The vaccine is to be used only before its 'expiry' term has expired and if the intactness of the ampoule is preserved and the vaccine looks normal. The vaccine looks normal if it is with yellow to orange over-suspension liquid and whitish suspension, which when shaken homogenises – to opalescence without aggregated particles.

When the ampoule is opened and the injection is made with all the necessary requirements for antiseptics.
If persons with hypersensitivity are immunised, antihistamine preparations must be prescribed together with the immunisation, at the discretion of the physician.

The vaccine must NOT be made intravenously

MEDICAL INTERACTIONS AND OTHER FORMS OF INTERACTIONS

After the application of gammaglobulin specific for CHF, if immunisation with CHF vaccine is necessary, 30 days should pass. In case of corticosteroid preparations use or immunosuppressive treatment, when according to vital indications, it is possible that the vaccination may turn out unsuccessful. This necessitates establishing the protective status (availability of complement-binding antibodies) with the view of a possible continuation of the immunisation with CHF vaccine.
No interactions with alcohol, tobacco and foods are described.

SPECIAL PRECAUTIONS CONCERNING USE BY SPECIFIC GROUPS OF PATIENTS (CHILDREN, PREGNANT AND BREAST-FEEDING WOMEN, ELDERLY PATIENTS, PERSONS IN SPECIFIC PATHOLOGICAL CONDITIONS)

No tests have been carried out for possible teratogenic action of the medicinal product during pregnancy, thus the vaccine is not recommended in such cases. For breastfeeding – no side interactions of the medicinal product have been described in the practice.

INFLUENCE ON THE ABILITY TO DRIVE AND OPERATE MACHINES

There are no data for influence on the ability to drive and operate machines.

DATA FOR AUXILIARY SUBSTANCES THAT ARE TO BE KNOWN REGARDING THE PRODUCT SAFETY

Thiomersal – may cause allergic reaction.

INFORMATION ON THE CORRECT USE

DOSAGE AND MODE OF APPLICATION:

1 ampoule = 1ml = 1 dose

Before use shake energetically the ampouled vaccine until it turns into homogeneous suspension. The vaccine from an open ampoule is to be applied immediately deep subcutaneously in the area of the shoulder blade under its lower edge.

PRIMARY IMMUNIZATION

Two injections of 1 ml (one dose) with an interval of 30 – 45 days.

REIMMUNISATION
The first reimmunisation is to be done with one injection of 1 ml (one dose) 1 year after the first application and then every 5 years.
<i>It is advisable that the immunisation starts in the pre-epidemic period (March-April).</i>
DURATION OF THE TREATMENT WHEN IT HAS TO BE RESTRICTED
See Reimmunisation
WHAT TO DO IN CASE OF OVERDOSE (SYMPTOMS, EMERGENCY MEASURES)
No overdosing is allowed.
WHAT TO DO IN CASE OF MISSED DOSES
The course shall be started anew – with the primary immunisation.
INSTRUCTIONS IN CASE OF NECESSITY, WHEN DISCONTINUING THE PRODUCT USE IS CONNECTED WITH RISKS
In case of tick bite and temperature over 37.5°C, immediately apply specific CHF-bulin.
UNDESIRE SIDE REACTIONS:
The application of CHF vaccine may be accompanied with local and general reactions of the organism. The local reactions manifest themselves in slight reddening of the place of injection. The general reaction may manifest itself in an increase of the body temperature up to 37.5°C.
STORAGE
ANTI-CHF VACCINE should be stored and transported between +2°C and +8°C IT MUST NOT BE FROZEN. Keep away from children.
SHELF LIFE
The vaccine has an expiry term of 24 months as of the date of production, printed on the package. Never use a vaccine with an expired term.
NAME AND ADDRESS OF MANUFACTURER
BB - NCIPD Ltd. BULGARIA 1504 Sofia, 26 Yanko Sakazov Blvd. Tel.: +359 2 944 61 91 Fax: +359 2 943 30 75 E-mail: bulbio@bulbio.com

Appendix 5: Ribavirin

Source: The WHO Essential Medicines Library, available from: <http://www.who.int/emlib/> (accessed on 18 February 2009)

MODEL LIST INFORMATION			
SECTION	FORMULATION	DISEASE/INDICATION	RATIONALE FOR INCLUSION
06.04.03.00 Other antivirals	Dosage form and strength Injection for intravenous administration: 1000 mg and 800 mg in 10-ml phosphate buffer solution. Oral solid dosage forms: 200 mg; 400 mg; 600 mg. ATC Code Type of List Core List		Date added: 2007.
MODEL FORMULARY INFORMATION			
GENERAL INFORMATION			
<p>Also known as Tribavirin</p> <p>Haemorrhagic fever virus infection</p> <p>Ribavirin (tribavirin) inhibits a variety of DNA and RNA viruses. It is active against viral haemorrhagic fevers caused by the Arenaviridae and Bunyaviridae family viruses, which include Lassa fever, Argentine haemorrhagic fever, Crimean-Congo haemorrhagic fever and haemorrhagic fever with renal syndrome. Treatment of Lassa fever is most effective if started within 6 days of the onset of fever. Other indications for ribavirin include the treatment of respiratory syncytial virus infection, and with peginterferon alfa or interferon alfa for the treatment of chronic hepatitis C infection (consult manufacturer's literature for treatment details).</p> <p>Uses: treatment of haemorrhagic fever, including Lassa fever, Argentine haemorrhagic fever, and Crimean-Congo haemorrhagic fever; haemorrhagic fever with renal syndrome</p> <p>Contraindications: pregnancy (teratogenic risk; see note below and Precautions); breastfeeding; severe cardiac disease, including unstable or uncontrolled cardiac disease in previous 6 months; haemoglobinopathies (including thalassemia or sickle-cell anaemia), haemoglobin levels less than 8 g/dl; severe debilitating medical conditions; severe hepatic dysfunction or decompensated cirrhosis of the liver; autoimmune disease (including autoimmune hepatitis)</p> <p>PREGNANCY. Risk of serious foetal abnormalities exists when ribavirin is used during pregnancy, but because of the high risk of mortality from haemorrhagic fevers for both pregnant women and the foetus, maternal benefit should be considered. Lassa fever is especially severe late in pregnancy, with maternal death or foetal loss occurring in more than 80% of cases during the third trimester.</p> <p>Precautions: for woman or man, contraception during and for at least 7 months after treatment; renal impairment; monitor blood counts at least weekly.</p> <p>Dose:</p> <p>Haemorrhagic fevers, <i>by mouth</i>, ADULT initially 2 g then 1 g every 6 hours for 4 days, then 500 mg every 6 hours for 6 days; CHILD initially 30 mg/kg then 15 mg/kg every 6 hours for 4 days, then 7 mg/kg every 6 hours for 6 days</p> <p>PATIENT ADVICE. Oral ribavirin should be taken with food</p> <p>Haemorrhagic fevers, <i>by slow intravenous infusion</i> (over 10–15 minutes), ADULT initially 17 mg/kg (maximum 1 g) then every 6 hours for 4 days, then 8 mg/kg (maximum 500 mg) every 8 hours for 6 days; CHILD initially 17 mg/kg then every 6 hours for 4 days, then 7 mg/kg every 8 hours for 6 days</p> <p>Haemorrhagic fever with renal syndrome, <i>by slow intravenous infusion</i> (over 10–15 minutes), ADULT initially 33 mg/kg (maximum 1 g) then 16 mg/kg (maximum 1 g) every 6 hours for 4 days, then 8 mg/kg (maximum 500 mg) every 8 hours for 6 days</p> <p>Adverse effects: haemolytic anaemia, neutropenia, thrombocytopenia, aplastic anaemia; myocardial infarction, arrhythmias; infections; nausea, vomiting, diarrhoea, colitis, anorexia, fever, rigors, dyspnoea, cough, dizziness, insomnia, myalgia, arthralgia, fatigue, headache, impaired concentration, irritability, anxiety, depression, suicidal ideation (more frequent in children), autoimmune disorders, pulmonary toxicity, pancreatitis, diabetes, hypothyroidism, hyperthyroidism, retinal haemorrhage, retinal thrombosis, alopecia, pruritus, rash, rarely hypersensitivity reactions.</p>			